

Summary of Health Research on Ultrafine Particles

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The University of Washington conducted a study of ultrafine particles in areas in and around SeaTac, WA. A report of their study will be available by the time this report is published. *UW Study Citation: Austin E, Xiang J, Gould T, Shirai J, Yun S, Yost MG, Larson T, Seto E. Mobile Observations of Ultrafine Particles (MOV-UP) Study Final Report. University of Washington, December 2019.*



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Executive Summary

Particulate matter (PM) is any particle in the air. It can come from sources like dust, coal, cars, and airplanes. When people inhale these particles, health problems can occur. How this affects health depends on how many particles are in the air, as well as on the size, mass, and surface area of the particles. There are various sizes of particles; PM₁₀ and PM_{2.5} include larger particles, while ultrafine particles (UFPs) are the smallest fraction of PM. There is concern that UFPs can cause more health problems than larger particles. This report examines the link between UFPs and health. The Washington State Department of Health drafted it at the Port of Seattle's request. The goals are to provide a summary of the science on UFPs and health, to discuss UFPs that come from airplanes, and to make recommendations for future research.

UFPs have many unique qualities that make them possibly more harmful to human health than larger particles. UFPs are able to travel deeper into the lung than larger particles. They are also small enough to avoid the body's attempts to clear particles from the lungs, allowing them to stay in the body longer, to build up, and to cause damage. They can also move from the lungs to the bloodstream and to other organs.

Certain groups of people are more sensitive to UFP exposure. These groups include people with pre-existing heart and lung disease, infants, older adults, people with diabetes, communities with a lower socio-economic status, and pregnant women. Emissions from large airports can lead to higher UFP concentrations inside nearby buildings or houses, resulting in possible human exposure.

Exposure to PM₁₀ and PM_{2.5} negatively affects the heart, lungs, brain, and nervous system. They are also associated with stroke, type 2 diabetes, and pre-term and low birthweight babies. With respect to UFPs, increasing evidence from animal studies suggests exposure can have adverse health effects in humans.

Most of what we know about possible health effects from UFP exposure comes from research done on animals. Strong and consistent evidence from animal studies indicates long-term exposure to UFPs is related to negative effects on the brain, nervous and respiratory system. A few animal studies have reported that UFPs can also affect reproduction and development. Future work will help us interpret how these data can be translated to humans so as to provide public health guidance.

To understand the effect of UFPs on human health, we recommend more studies. Along with increasing UFP air monitoring across the country to gather more data on air concentrations, recommended areas of study include learning more about the makeup of UFPs related to toxicity, improving methods for measuring and modeling UFP concentrations and human exposure across time and space, and using consistent methods and study designs that account for other pollutants that can negatively affect health.

INTRODUCTION

The Washington State Department of Health wrote this report at the request of the Port of Seattle. It aims to summarize recently published literature on the association between ultrafine particulate (UFP) matter exposure and health effects. A growing body of literature evaluates the role of UFP exposure on adverse health outcomes. Concern exists that these small particles could have a greater effect on health than larger particles.

The objectives were to provide a summary of the current scientific literature regarding UFP exposure and health, to discuss aviation-related exposures, to identify gaps in the literature, and to make recommendations for additional studies or research.

Three reports that provide a comprehensive summary and evaluation of ultrafine particles were main sources of information: The Integrated Science Assessment for Particulate Matter (ISA PM (2009)) published by the U.S. Environmental Protection Agency (US EPA) in 2009 [1], Understanding the Health Effects of Ambient Ultrafine Particles (UFPs) (HEI UFP Report (2013)) by the Health Effects Institute in 2013 [2], and Health effects of ultrafine particles: A systematic literature review update of epidemiological evidence [3]. Where possible, additional references were incorporated to provide more information.

We also examined the draft Integrated Science Assessment for Particulate Matter (ISA PM 2018) report released by EPA for public comment on October 2018. EPA has not formally disseminated this draft report, and it does not represent EPA policy. This published draft is an update to the ISA PM (2009) and is undergoing revision. The Chartered Clean Air Scientific Advisory Committee (CASAC) has reviewed the draft and provided comments. A brief summary of main findings is described in the ultrafine particles and health section. More information is at: www.epa.gov/isa.

The University of Washington conducted the *Mobile Observations of Ultrafine Particles (MOV-UP) Study* in areas in and around SeaTac, WA. A report of their study will be available by the time this report is published.

ULTRAFINE PARTICLES

Ambient air pollution is a complex combination of suspended particulate matter (PM) and liquid particles. Particulate matter is classified by the size of particle. Environmentally monitored particle size fractions include coarse particles or PM₁₀ (aerodynamic diameter < 10 micrometer [μm]), fine particles or PM_{2.5} (aerodynamic diameter <2.5 μm) and ultrafine particles (PM<0.1 μm). The relative sizes of these particles are illustrated in Figure 1. Ultrafine particles are generally measured by particle number concentration (PNC), which is the total number of particles per unit volume of air [2]. Ultrafine particles are the smallest fraction of PM and are the prime contributor to a particle number measurement, while making little contribution to particle mass measurements. Nanoparticles (NPs), are similar to ultrafine particles in being particles with diameters between 0.001 and 0.1 μm, but they are human-engineered particles typically with specific intended purposes such as nanotubes, nanofibers, nanowires, etc.

Ultrafine particles can originate from many sources and are generally related to combustion processes. Mobile sources include emissions from vehicles, ships, and airplanes. Stationary sources include power plants, incinerators, metal fumes (smelting, welding, etc.), and biomass burning [4, 5]. Vehicle exhaust, brake wear, rail, metro, metal processing and power generation plants can release iron and other metal NPs in abundance in the surrounding air [6]. UFPs can also originate from natural sources including

wind-blown mineral dust, forest fires, volcanoes, vegetation, and oceans [1]. Motor vehicles (both diesel and gasoline) are primary contributors of UFP emissions and a significant source of human exposure [2, 7-10].

In 2004, four main emission sources were identified in the Seattle area: diesel engine emissions, motor vehicle emissions, wood burning, and secondary aerosol production [11]. Secondary aerosols are formed from chemical reactions when primary pollutants mix in the air [1]. Recently, the Olympic Region Clean Air Agency (ORCAA) identified wood heating as a main source of UFP emission in Port Angeles, Wash. PM_{2.5} and UFP concentrations were highest during the winter months (January and February) [12]. This is consistent with another study that found levels of both PM_{2.5} and UFP increased during the winter months due to residential heating with woodstoves and fireplaces [13].

Emissions from marine and commercial aircraft jet engines are also important sources of UFP pollution. Most particles emitted by plane and marine engines are in the ultrafine size range (< 0.1 μm) [14-17]. Aviation-related UFP emissions appear to occur especially during landing, takeoff, or idling activities at airports, and can contribute a high number of particles over large areas downwind [18-25]. For example, researchers found UFP concentrations four to five-fold higher than typical levels at distances eight to 10 kilometers from several airports [26-28]. A few studies have shown that particles released by jet airplanes [18, 19] disperse in a manner similar to particles released by freeway traffic [29].

In urban areas, the size, shape, chemical composition, and concentration of UFPs can vary with distance from the source, time of day, and season [1, 30]. Near roadways, the highest concentrations of UFPs are found near high-traffic corridors [31-34], and the UFP concentrations decline with distance from the highway [35]. For example, near a major interstate in Los Angeles the highest concentration of the smallest particles was closest to the roadway. As distance from the road increased, the concentration of small particles rapidly decreased and transitioned to larger particles until blending into background levels at 300 meters [2]. Particle concentrations have also been found to spike when vehicles accelerate after stopping [8, 36]. In general, UFP levels appear to be much higher during the evenings, and winter months, compared to summer and spring [8, 37-42]. Higher levels of UFPs are also associated with lower humidity [43, 44].

Physical and Chemical Characteristics of Ultrafine Particles

UFPs have unique physical and chemical (PC) properties compared to larger particles. These properties may lead to differences in health effects [45-56]. Particle size is a major determinant of the fraction of inhaled particles depositing in and cleared from various regions of the respiratory tract [1].

UFPs have a higher surface area to mass ratio than larger particles. This means the ratio of surface area to the total number of atoms or molecules increases exponentially as particle size becomes smaller. This results in a larger relative surface area of smaller particles that adsorb relatively higher amounts of toxic air pollutants (e.g., oxidant gases such as ozone, nitrogen oxide, organic compounds, and transition metals). Large surface area is important because the surface of solid particles (e.g., atoms or molecules) interact with cell membranes and subcellular structures, leading to specific biological and toxicological responses.

Selected studies attribute adverse health effects of UFPs with high particle number per unit mass and reactive surface [57-63], particle size [45, 47, 51, 64, 65], surface area [52-55, 66, 67], and surface chemistry [68-74].

The small size and large specific surface area give them unique properties, providing for a potential to cause adverse effects [62]. There is neither a clear picture of which PC characteristics are most important

to consider for UFPs nor agreement on which PC characteristics (e.g., mass, number, size, or surface area) are the most suitable dose metric (i.e., information about the actual dose to target cells) for identifying exposure to UFPs.

Ultrafine particle deposition, retention and distribution

People are most commonly exposed to UFPs through inhalation. They can also be exposed through the skin or by ingestion. The PC properties of UFPs influence how they interact with the respiratory system once they are inhaled. In general, UFPs deposit deeper in the lung, they are cleared from the respiratory system more slowly, and they are more efficiently distributed to the bloodstream and organs than larger particles. The HEI UFP Report, the PM ISA 2009 [1, 35] and others [32, 62], detail the process of UFP deposition, retention and distribution. Here we provide a brief overview of these processes.

When air is inhaled it starts in the nasal cavity and moves through to the larynx, trachea, bronchus, bronchiole, and ultimately to the alveoli regions deep in the lungs where gas exchange occurs (Figure 2). The site of deposition for a particle is related to particle size [62]. Models on deposition fraction predict that UFPs deposit with the highest efficiency in the bronchioles and alveoli. Larger particles (two to 10 μm) preferentially deposit higher in the respiratory tract; in the trachea and bronchi (Figure 2) [35]. The deposition of UFPs depends on diffusion, which leads to a more homogenous distribution compared to larger particles. Larger particles deposit mainly based on particle impaction and gravitational settling. The site of deposition also depends on particle movement, the geometry of the lungs, and the movement of gas flow [75]. Other factors such as exercise, oral versus nasal breathing, disease status, body mass index, sex, and age can also affect UFP deposition in the respiratory tract [76-79]. High-deposition efficiency in healthy subjects [76, 80-86] is observed and gets worse in those with chronic inflammatory respiratory disease such as asthma and chronic obstructive pulmonary disease (COPD) [62, 87, 88].

When deposited particles are not cleared from the respiratory system, accumulation of particles and accompanying inflammation are more likely to occur [62, 89-91]. Large particles are generally cleared from the respiratory tract by physical (e.g., the mucus, macrophage phagocytosis¹, epithelial endocytosis², etc.) and chemical processes (e.g., dissolution, leaching, protein binding) [35]. The majority of inhaled ambient particles are cleared by mucociliary clearance³ [92], a process that removes microbes and debris from the airways. Mucociliary clearance is less effective at removing UFPs because these small particles can penetrate through the mucus or into the alveolar region where mucus is absent. This leads to long-term particle retention, which can result in accumulation in the airway tissue. In the bronchioles and alveoli, the major clearance mechanism results from particle phagocytosis by alveolar macrophages. Scientists recognize today that UFPs can escape macrophage attack because of the inability of these cells to engulf tiny particles [63, 93]. Only a low percentage of nanosized particles (< 0.1 μm) deposited in the alveolar region are taken up by alveolar macrophages [62]. Scientists have found that UFPs have slower clearance rates than larger particles [94]. For example, a recent study found minimal clearance for inhaled 100 nm size carbon particles 24 hours after exposure. Particles were retained in the lung periphery and in the conducting airways [88].

Another unique characteristic of UFPs that affects health is their ability to translocate from the lung into the blood. Once inhaled, UFPs rapidly enter the circulatory system with the potential to directly affect the vascular system. For instance, UFPs cross the alveolar-capillary barrier in the lungs, reaching organs such

¹ Macrophages are a type of white blood cell that engulfs and digests foreign objects. Phagocytosis, process by which certain cells called phagocytes ingest or engulf other cells or particles.

² Endocytosis is the uptake of material into a cell by an invagination of the plasma membrane and its internalization in a membrane-bounded vesicle.

³ The term “clearance” is used here to refer to the processes by which deposited particles are removed by mucociliary action or phagocytosis from the respiratory tract.

as the liver, spleen and heart [88, 95-102]. They also bypass the blood brain barrier [103], reaching the central nervous system [104, 105]. Translocation⁴ of inhaled UFPs has been demonstrated in animal studies for a range of UFPs [104-111]. Translocation of UFPs is likely to occur in humans, although it is difficult to observe directly [112].

ULTRAFINE PARTICLES AND HEALTH

There has been extensive research on the health effects of both PM_{2.5} and PM₁₀ [113-117]. Increasing evidence indicates PM_{2.5} and PM₁₀ exposures lead to declines in lung function, and to worsening of heart and lung diseases that may result in hospitalizations or death, stroke, type 2 diabetes, neurological and cognitive impairment, and pre-term and low-birth weight babies, among other effects [111, 118-122]. While there is less information on health effects of UFPs, some studies have tried to distinguish the effects of coarse particles and fine particles. Several of these studies have found that more of the health effects were related to PM_{2.5} particles than the coarse particles, and the elevated effect of coarse particles was not often significant after accounting for PM_{2.5} particles [117, 123-125]. Table 1 presents a summary of the evidence on the health effects associated with exposure to UFPs.

Much of what we know about UFPs and health effects is based on toxicological and animal studies. Studies have used UFPs as well as nanoparticles (e.g., carbon black, titanium dioxide, cerium oxide, gold, silver), to assess health effects in animals. Based on PC properties, researchers have determined that UFPs behave similarly to nanoparticles (i.e. induce similar biological responses) [62, 75, 126].

The body of epidemiological literature on the relationship between health and UFP exposure is limited, but growing. Increasing evidence suggests UFP exposure can cause adverse health outcomes; however, it is not clear whether short- and long-term UFP exposure in humans can induce adverse health effects to the same extent as those observed in animals [32, 127].

The primary epidemiological and toxicological findings from several comprehensive recent reports are briefly described here.

The ISA PM (2009) determined that the evidence suggested a causal relationship between short-term exposure to UFPs, and respiratory and cardiovascular effects. This conclusion was based on limited epidemiologic evidence from hospital admissions and emergency department visits involving respiratory-related diseases, respiratory infection, and asthma exacerbation [1]. Recent short-term studies published since the ISA PM (2009) reported an association between UFP exposure and asthma hospital admissions, asthma exacerbation [128, 129], and decreased lung function in people with asthma [130, 131]. However, another study conducted in five European cities reported no association with asthma hospital admissions [132]. The evidence was inadequate for effects from long-term exposure [1].

The HEI UFP Report (2013) determined that epidemiologic findings provided suggestive evidence of short-term exposure to ambient UFPs on acute mortality and morbidity from respiratory and cardiovascular disease [35]. Recent epidemiological studies have not provided consistent findings of the cardiovascular or respiratory effects from exposures to ambient UFP [133-137]. Findings from animal studies indicated that UFPs can induce airway inflammation, although the concentrations of ambient UFPs necessary to induce an inflammatory response were not known and may exceed the relatively high concentrations found on a busy roadway [35].

⁴ The term “translocation” is used here mainly to refer to the movement of free particles across cell membranes and to extrapulmonary sites.

Authors of the ISA PM (2018) draft report reviewed recent epidemiological and experimental studies to build upon the ISA PM (2009). These studies examined the relationships between UFP components, sources, exposures, and short- and long-term respiratory, cardiovascular, nervous system, and cancer health effects, as well as mortality. Based on the studies examined in the the draft report, scientists determined that the evidence is “suggestive, but not sufficient to infer a causal relationship” between UFP exposure and respiratory and cardiovascular health effects [112]. For effects on the nervous system, the draft ISA PM (2018) reports a “likely causal relationship” with UFP long-term exposure based on evidence in animals [112]. The authors also determined that it is difficult to interpret the epidemiologic results based in part on differences in methods including particle size ranges examined, spatial and temporal variation of UFP emissions, and the use of different exposure metrics [112].

The German Environmental Agency published a systematic review in 2019 with the objective of updating the 2013 HEI report. Its review included 85 epidemiological studies investigating health effects of UFPs for the period January 1, 2011 until November 5, 2017 [3]. Due to limitations in study designs, it could not conclude that short-term exposure to UFPs had an effect on morbidity or mental health outcomes. It found evidence that children and people with pre-existing cardiovascular conditions could be more susceptible. It also found evidence for an association with short term UFP exposure and increased blood pressure.

Investigating the health effects from UFP exposure is an increasingly active area of research. One overarching landmark study that will shed light on this area is the adolescent brain cognitive development (ABCD) study [138]. This study, already initiated, is the largest long-term study of brain development and child health in the U.S. The study design includes investigations by researchers across numerous disciplines on the effects of PM_{2.5} particle pollution on brain development. This longitudinal cohort study will follow children 9 years of age for 10 years and will improve our understanding of the role environmental factors, such as UFP exposure, have on childhood development.

Specific Health Endpoints

Oxidative Stress and Inflammation

Long-term studies on mice exposed to UFPs provide evidence of inflammation and oxidative stress in the brain such as in the hippocampus and cerebral cortex [45, 47, 55, 139-144]. Inflammation has been linked to a number of health-related outcomes. Oxidative stress can result in damage to healthy cells and blood vessels, and a further increase in the inflammatory response. Evidence suggests that UFPs can translocate from the nasal olfactory epithelium to the olfactory bulb in the brain via the olfactory nerve (nose-to-brain route) [6, 106, 107, 145]. Limited evidence from controlled human exposure studies indicates that UFP exposure increases systemic inflammation, oxidative stress and other markers of vascular function (this could rupture plaques and obstruct blood flow to the heart) [146, 147].

Nervous System Effects

Exposure to air pollution, specifically PM_{2.5}, has been linked to numerous effects including delays in psychomotor development, lower IQ in elementary school children, increased risk for autism, greater anxiety, depression, and attention-deficit related problems during childhood [1]. Animal data indicate that the UFP fraction of ambient PM is associated with adverse neurological effects. It has been suggested that UFP may represent the more potent fraction of ambient particulate matter [148, 149].

Multiple components of air pollution (e.g., diesel exhaust, fine as well as UFP, and toxicants adsorbed to particles), can produce inflammatory changes in the brain. Selected animal toxicological studies provide

evidence of inflammation and oxidative stress in the brain with exposure to UFPs [1, 47, 55, 139, 140, 143, 144, 150-154]. Many controlled laboratory animal studies linked exposure to UFPs with adverse effects on brain development, including changes in behavior and deficits in intelligence and memory. Specific examples include: neurodegeneration in mice exposed to particles less than 0.2 μm in size [139, 145, 155]; neuro inflammation in animals during the early process of development [151, 152, 156, 157]; changes in learning, memory, and behavior in pre- and post- natal exposed animals [153, 158-160]; and changes in locomotor activity and altered levels of neurotransmitters⁵ (dopamine, norepinephrine) in mice exposed in utero to a low concentration of diesel exhaust [161]. Human studies have not found an association between UFP exposure and nervous system effects.

Since the release of the draft ISA PM (2018), additional toxicological data have become available about nervous system effects from UFP exposures [139, 152, 153, 155-158, 162-166]. Here we present a brief summary of selected studies.

A longitudinal study assessed the association of UFP exposure with cardiovascular risk factors in an adult population, using modeling techniques adjusted for spatial variation and temporal trends [167]. While not addressing possible confounding from other co-pollutants, the authors identified an association of blood pressure and markers of systemic inflammation with exposure. Systemic inflammation is considered a critical outcome in the pathway to neuro-inflammation [1].

Gestational exposure to polluted air from filtered diesel exhaust (nanoparticles < 500 nm) in a rabbit model was conducted to advance previous findings that maternal exposure to these particles affects fetal development [106]. This study showed nanoparticles in olfactory tissues of offspring exposed prenatally that were associated with changes in olfactory-based behavior. The findings suggest that these particles could be translocated to the fetal nervous system structures, possibly leading to pathological changes within the nervous system. Klocke and co-researchers investigated neurological effects in offspring of mice exposed to concentrated ambient UFP and PM_{2.5} levels during pregnancy. The goal was to determine if embryogenesis was a sensitive period such that exposure could lead to impaired brain development [157, 164]. Neuropathological changes were observed postnatally and particular changes remained through brain maturation, suggesting that exposure to UFP and PM_{2.5} during early brain development leads to irreversible changes in the developing brain [157, 164].

Exposure to low levels of UFPs during early postnatal period produced deficits in cognitive function in adult male mice. The evidence of behavioral effects from neurodevelopmental impact were not evident [165]. Cory-Slechta and co-researchers observed sex-specific cognitive and behavior changes in a study of mice exposed postnatally to low-level concentrations of ambient UFP [166]. These findings are consistent with previous findings discussed in the draft ISA PM (2018) [112].

To understand the interpretation of rodent model results from which the draft ISA PM (2018) garnered a causal relationship between UFP exposure and nervous system effects, researchers developed a quantitative tool to predict inhaled UFP dose to human and rodent (e.g. rat) nasal olfactory regions. They determined that the dose of inhaled particles in the human and rat olfactory region was influenced by particle size and breathing rate [168].

⁵ Neurotransmitter - a chemical substance that is released at the end of a nerve fiber by the arrival of a nerve impulse and, by diffusing across the synapse or junction, causes the transfer of the impulse to another nerve fiber, a muscle fiber, or some other structure. For example, norepinephrine transmits nerve impulses across a synapse.
<https://www.merriam-webster.com/dictionary/neurotransmitter>

These more recent publications are generally in line with the conclusions of the draft ISA PM (2018).

Respiratory effects

Results from studies of both short- and long-term exposure suggest that UFPs may affect the respiratory system [128, 129, 132, 169, 170]. Effects include increases in lung inflammation, allergic response, and decreased lung function. For example, long-term studies have found increases in markers of injury, and changes in levels of oxidative stress [140, 171], while some short-term animal studies indicate that exposure to UFPs enhance allergic reactions [150, 172].

Cardiovascular effects

The HEI UFP report (2013) indicates that available animal data are insufficient to establish a clear link between short-term exposure and cardiovascular effects [35]. The German Environmental Agency determined there is evidence of adverse short-term associations with inflammatory and cardiovascular changes. It suggested these changes may be at least partly independent of other pollutants [3].

A short-term (four hours) inhalation study in mice exposed to UFPs resulted in no appreciable changes in heart function. However, when mice were exposed to UFPs plus ozone, it caused a significant decrease in cardiac contraction 24 hours after exposure [173]. A 2015 study found increased levels of IL-6 in lung tissue in rats exposed to UFPs for several days. Short-term exposure to UFPs resulted in upregulation of genes encoding angiotensin 1 receptor and kallikrein-1 (KLK-1). The angiotensin and KLK-1 system are important endocrine systems that regulate cardiovascular physiology. Both systems control cardiac muscle contraction, and vasodilation [68]. Both studies did not report significant changes of impaired heart function.

A study of people with type 2 diabetes and impaired glucose tolerance living in urban areas identified changes in heart rate variability to be associated with personally measured particle number concentration and ambient PM_{2.5} [174]. A study in California assessed ischemic heart disease mortality incidence among more than 100,000 women for six years (2001 to 2007) in association with UFPs, hazardous materials (e.g., metals), and mobile sources [175].

A recent study conducted in Mexico City found iron-rich nanoparticles (< 0.1 µm) in heart tissue of young adults. Heart tissue in subjects contained two to 10 times more NPs than the control subjects [176]. These particles were found in many different cell structure such as the endothelium, myocytes, and mitochondria. Exposure to these particles appear to be associated with significant inflammation, which could potentially lead to severe health outcomes such as heart disease or heart failure.

Reproductive and developmental effects

Animal studies suggest that inhalation of UFPs could lead to reproductive and developmental effects [177-179]. Two recent animal studies provide suggestive evidence of reproductive and developmental effects in mice and rabbits exposed to diesel exhaust particles pre- and postnatally [180, 181]. One study demonstrated autism spectrum disorder related behavioral changes in mice [180]. Another study showed an increased sperm DNA fragmentation rate in male rabbits exposed daily to diluted diesel exhaust gas during gestation [181]. However, uncertainty remains (for example, mechanisms responsible for these modifications and their physiological consequences) when evaluating the evidence of these health endpoints.

Although some toxicological studies indicate changes in male reproductive function (e.g., increased testosterone levels, testicular cholesterol, and activation of biomarkers relating to testicular cholesterol biosynthesis), the evidence is inadequate to infer a causal relationship from UFP exposure on male

reproduction and fertility. The data were also considered inadequate to establish a relationship with pregnancy and birth outcomes [178, 179].

Cancer

The ISA PM (2009) determined that the epidemiological evidence was inadequate to establish a relationship between long-term exposure to UFPs and cancer [1]. Since the ISA PM (2009), few recent studies examined UFP exposure and cancer [147, 182-187]. From these studies, there is inadequate information to establish a relationship between long-term exposure to UFPs and cancer. Along with the limited available study numbers, the lack of adequacy to establish a relationship was due to study limitations (e.g., uncertainty in the spatial/temporal variability, exposure measurement errors, underestimation of exposure levels, etc.).

Total mortality

The HEI UFP Report concluded there was inconsistent evidence to identify a relationship between UFP exposure and acute morbidity and mortality from respiratory and cardiovascular disease [35]. The findings were based on limited epidemiological evidence. Further, there was inconsistency in epidemiologic study results for cardiovascular and respiratory morbidity.

Vulnerable populations

People with a pre-existing lung or heart disease such as asthma, COPD and cardiovascular disease may be more sensitive to the effects of UFP exposure [62, 87, 88]. In people with COPD, the deposition of UFPs increases with particles smaller than 0.1 μm diameter because of the narrowing of the airways, and other possible mechanisms⁶ [87]. Vulnerable groups include infants, older adults, people with diabetes, and people within communities of lower socioeconomic status⁷ [188] as they have been shown to be more exposed than other groups. Also, some people may have a genetic predisposition that increases susceptibility to the effects from UFP exposure [1].

The developing fetus is particularly sensitive to air pollutants, as some pollutants are able to cross the placental membrane and reach vital organs during fetal development. Children exposed in early childhood to combustion-related air pollutants are also a sensitive group. UFP exposure may affect cognitive abilities, academic performance, and consequent educational trajectories of children – and consequently, their long-term health, wealth, and social status in adulthood [189, 190]. Children receive higher doses of UFP than adults because they have less nasal particle deposition than adults do; they inhale more air relative to their body size than adults and they tend to breathe through their mouths more, which is less efficient than the nose for removing inhaled particles.

Populations Living Near an Airport

Emissions from motorized vehicles and from aircraft turbine engines are primary sources of elevated UFP exposures at airports and surrounding areas [19, 20, 25-28, 191-196]. Recent work has expanded and supported earlier findings that airports are leading sources of UFPs, and that UFP emissions can result in increased indoor air concentrations in surrounding areas. For example, some researchers recently looked

⁶ Possible mechanisms for increased deposition in airway obstruction include increased transit time of particles, abnormal expiratory collapse of airways due to flow limitation, and flow perturbations resulting from decreased airway caliber.

⁷ Low-income families and underserved racial/ethnic groups include those that disproportionately reside near major roadways and other sources of air pollution. Socioeconomically disadvantaged students experience a heavier pollution burden than the general student population.

at the effect of seven airports on school children in California. Researchers mapped the area and examined the extent of airport-related air pollution exposure in schools located within a 10-kilometer radius of each airport. They found out that 91.2 percent of the students attending schools within the 10-kilometer perimeter of the airports are exposed on average to less than one hour per day. An estimated 65,409 (8.7 percent) students experienced downwind time averages that range from one to six hours per day at school throughout the academic year with exposure to airport-related air pollution. A higher proportion (10.6 percent) of socioeconomically disadvantaged students experienced higher levels of pollution [188].

In addition to these recent findings, a randomized crossover study investigated adults with asthma who were exposed to UFPs emanating from Los Angeles International Airport (LAX) [197]. The non-smoking participants with mild to moderate asthma walked a pre-determined path downwind from, and near to, the airport twice with an investigator who carried a device to determine particle size and lung deposited surface area. In addition, a mobile device was used to measure particle number, black carbon, particle-bound polycyclic aromatic hydrocarbons (PAHs), ozone (O₃), carbon dioxide (CO₂) and particle matter mass (PM_{1, 2.5, 4, & 10}). The study design controlled for traffic-related UFP exposure for the subjects to the study site. No systemic or pulmonary inflammation or lung function metric was associated with UFP exposure with the exception of interleukin 6 (IL-6), which is a pro-inflammatory mediator. This association between IL-6 and UFP airport emissions suggests increased acute systemic inflammation could occur with continued UFP exposure in adults with asthma.

A recent study exposed mice to jet engine and commercial airport particles (range from 136 to 269 nm size) via intratracheal instillation. Pulmonary exposure to these particles induced acute pulmonary inflammation, and increased levels of DNA strand breaks. Results suggest that jet engine particles have similar PC properties and toxicity as diesel exhaust particles [198].

A cell culture study by Jonsdottir and co-workers (2019) exposed bronchial epithelial cells to aerosols containing UFPs emitted from a jet engine burning two fuel types at idle and under thrust [199]. Results suggest cell response from exposure was linked with fuel consumption and particle structure. Cytotoxicity, oxidative stress and pro-inflammatory responses in the bronchial epithelial cells were observed with short-term exposure to UFPs. In a separate *in vitro* study using bronchial epithelial cells, ambient PM_{0.25} (UFP) was collected downwind of LAX with results, even at low exposure concentrations, resulting in toxic effects such as oxidative stress, inflammatory mediator release and cell viability (cytotoxicity). These outcomes reflect the findings observed by Jonsdottir and co-workers [200]. This *in vitro* work provides evidence to the supposition that UFP deposition in the pulmonary tract could lead to pulmonary inflammation through oxidative stress or a pro-inflammatory response.

In both *in vitro* studies, the animal study, and the crossover investigation, evidence indicates that UFP exposure results in changes in the expression of a pro-inflammatory mediator. *In vitro* studies can provide useful data on the toxicity, and mode of action, and can help answer questions about the dose-response of UFPs. The Jonsdottir et.al, study investigated only primary aerosol exposure, while the other two studies included the effect of secondary aerosol exposure. Both primary and secondary aerosols can impact effect outcomes. For example, the consideration of a primary aerosol source only without the inclusion of a secondary aerosol source can lead to an underestimation of exposure [197, 201]. Despite the different sources of UFP exposure, these data further support the importance of airport air-emissions as a contributor, along with vehicular traffic, to the PM air pollution mixture that can impact public health.

Toxicological and Epidemiological Study Limitations

The limitations and uncertainties within the experimental and epidemiological studies conducted have made it challenging to draw firm conclusions regarding the association of UFP exposure with various health outcomes. Some of these deficiencies include the following:

- There is a lack of measurement on both the presence of other pollutants (co-pollutants, which can result in confounding) and the chemical composition of the constituents within studies.
- There is lack of epidemiological studies assessing the effect of UFP pollution around airports.
- Most studies have not accounted for the spatial and temporal variability of UFP size distribution and composition with distance from the source. This results in exposure measurement error.
- There is a lack of consistency across the chemical and cell-based assays regarding oxidative and inflammatory activity.
- There is uncertainty associated with inconsistencies in findings across studies.
- There are limitations in study design including small sample numbers with limited statistical power, short durations of exposure, no information on long-term personal exposure, and subjects not blinded to the type of exposure received.
- A limited number of controlled human exposure and toxicological studies examined UFPs alone or in combination with other measured pollutants.
- There is limited evidence from toxicological studies at relevant concentrations (i.e. concentrations reflecting ambient air levels).
- Evidence from studies of association of short- as well as long-term exposures to UFPs on health outcomes is inconsistent.
- There are no standardized methods for measuring UFP exposure. It is challenging to separate the potential health effects of UFP exposure from the potential health effects of other exposures associated with air pollutants such as PM_{2.5}, NO₂, CO, and ozone.
- There is uncertainty in the representativeness of UFP measurements assessed from a single monitoring location; most studies have quantified UFP levels from single measurements only.
- There is a lack of consensus on which UFP exposure metrics and size fractions to use in investigations. Exposure metrics of interest include particle number concentration, mass concentration, and surface area concentration. The use of different metrics makes cross-study comparisons challenging.
- Interpretation and comparison of *in vitro* studies can be challenging as they provide results from experiments that: used particles of different compositions, used different target cells, used various durations of exposure, examined different endpoints, and generally used elevated exposures that are not relevant to ambient exposures.

Regulating Ultrafine Particles

Regulations limit the contribution of sources of UFPs, such as through vehicle emissions requirements. These regulations are not specific to UFPs but are aimed at $PM_{2.5}$, which encompasses UFPs. The U.S. EPA National Ambient Air Quality Standards (NAAQS) do not classify UFPs as a criteria pollutant [202], though they are included in the $PM_{2.5}$ and PM_{10} fractions. However, these mass fractions under-represent UFPs. There is no standardized UFP measurement method or reporting mechanism, and there are no state or federal ambient air quality standards specifically for UFP levels [32, 127].

CONCLUSIONS AND RECOMMENDATIONS

It is difficult to assess the impact of UFP exposure on health outcomes in humans. Animal evidence indicates that UFP exposure is associated with adverse health effects, including neurological effects. There is strong and consistent animal data linking long-term UFP exposure with nervous system effects, and these effects are often correlated with multiple markers of neurotoxicity in animals. We know more about the health outcomes from exposure to the $PM_{2.5}$ fraction compared to UFPs. Little is known about the number, mass or concentration of the UFP constituents in $PM_{2.5}$ estimates from any particular location as particle levels are source-dependent. UFPs are not evenly distributed in the atmosphere. They tend to vary widely across space and time. In addition, UFPs have unique physical and chemical properties compared to larger particles that lead to differences in how they affect health.

We cannot conclude from the $PM_{2.5}$ studies in humans whether UFPs are a major factor in observed neurological and other health outcomes associated with $PM_{2.5}$ exposure. Collectively, toxicological, epidemiological and controlled human exposure studies do not yet provide evidence that UFPs are more potent than other PM size fractions. No studies directly link UFPs to human brain health. Enhanced modeling methods will allow for improvements in estimating the impact of UFPs on human health. Thus, the evidence on health effects in humans associated with UFP exposure remains inconclusive or insufficient for most health outcomes.

Future endeavors need to center on addressing the data gaps and limitations addressed above. In short, these included: identifying key characteristics that induce toxicity such as particle number concentration, chemical composition, and surface area; identify whether translocation beyond the lung occurs in humans; seek to include UFP air monitoring across the country as part of NAAQS; determine parameters for identifying variability in the spatial-temporal distribution of UFPs; identify standardized methods for measuring UFP exposure; and conduct controlled investigations that adjust for measured co-pollutants.

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Figure 1. The relative size of PM_{2.5}, PM₁₀, and ultrafine particles with a comparison to microbiological and other biological entities. Bodies visible by light and transmission electron microscopy are indicated, and the scale bar denotes the size range of the respective biological entities [92].

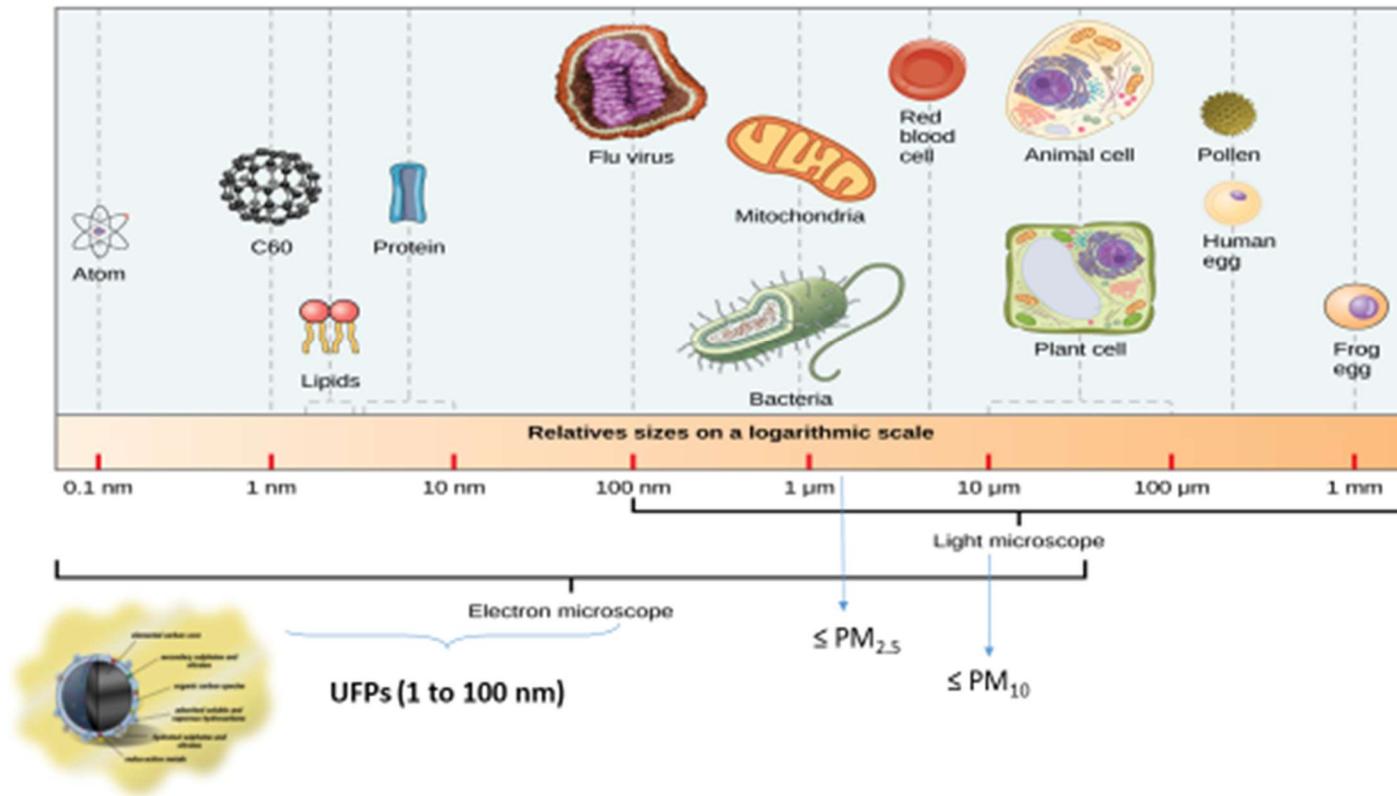


Figure 2. Deposition of coarse and ultrafine particles in the respiratory system (picture adapted from Poh et al. 2018) [92].

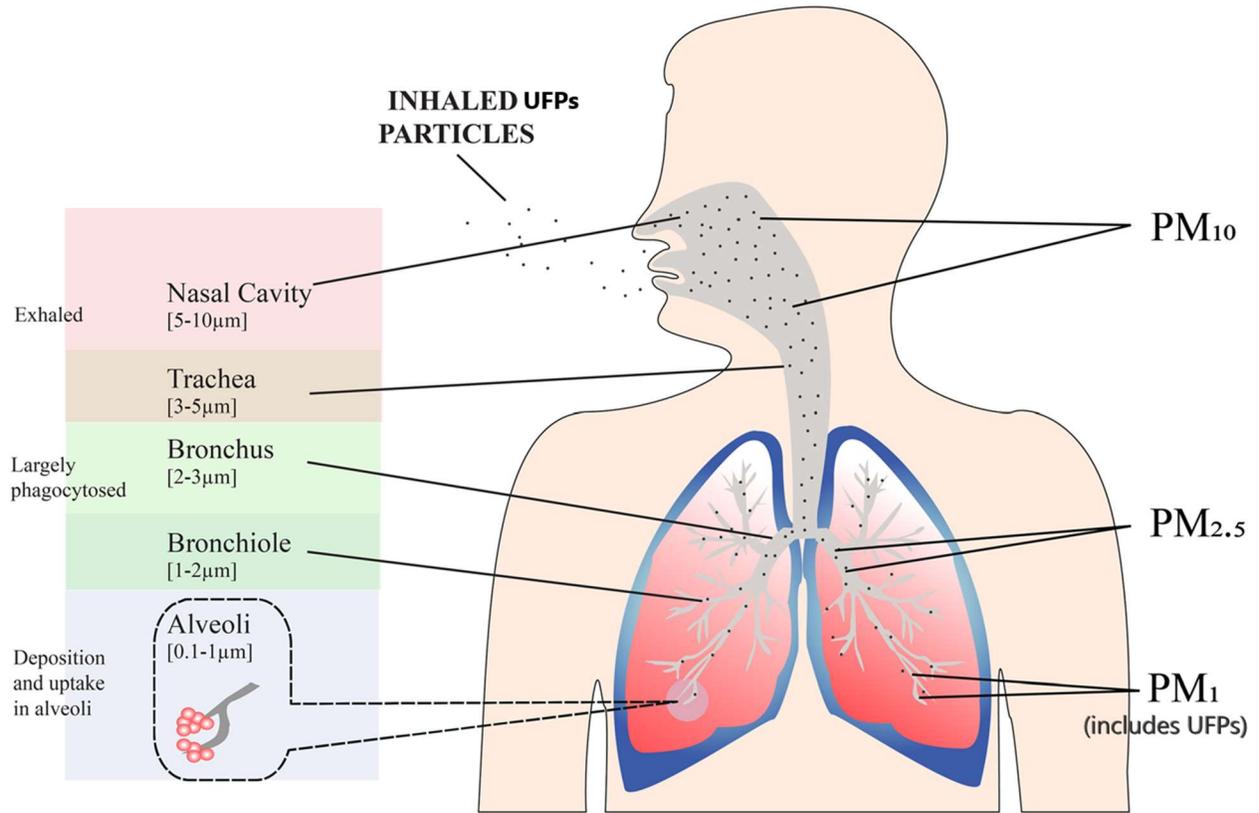


Table 1. A summary of health effects from long- and short-term ultrafine particulate matter exposure from the 2009 Environmental Protection Agency (EPA) Integrated Science Assessment (ISA) for Particulate Matter (PM), 2013 Health Effects Institute, 2016 UFP workgroup and the 2019 German Environmental Agency report.

	EPA PM ISA, 2009 [1]	Health Effects Institute, 2013 [35]	Workgroup on UFPs, 2016 [32]	German Environmental Agency, 2019 [3]
Respiratory Effects				
Short-term exposure	Suggestive of, but not sufficient to infer, based on limited epidemiologic evidence.	UFPs at high concentrations can induce airway inflammation (unknown the levels); responses in different species may vary, also differ by age; may enhance allergic response. Studies show inconsistent results, with some studies reporting associations with UFP exposure.	---	---
Long-term exposure	Inadequate	---	---	---
Cardiovascular disease (CVD) effects				
Short-term Exposure	Suggestive of, but not sufficient to infer, based on animal studies; few epidemiological studies did not provide strong support for an association of UFPs and effects on the cardiovascular system.	Animal data are insufficient, no clear evidence. Studies show inconsistent results, with some studies reporting associations with UFP exposure.	Negative association between UFP exposure and cardiovascular health including altered heart rate, heart rate variability, systemic inflammation, and changing microvascular function.	Children and people with pre-existing cardiovascular conditions could be more susceptible. Reported some evidence for an association with short-term UFP exposure and increased blood pressure.
Long-term exposure	Inadequate based on toxicological and epidemiological studies.	---	---	---
Nervous system effects				
Short-term Exposure	Inadequate, based on limited animal	Exposure to concentrated ambient UFPs near a roadway	---	---

	EPA PM ISA, 2009 [1]	Health Effects Institute, 2013 [35]	Workgroup on UFPs, 2016 [32]	German Environmental Agency, 2019 [3]
	toxicological studies.	has the potential to induce inflammation in the brain.		
Long-term exposure	Limited animal toxicological evidence. Lack of epidemiological studies.	---	---	---
Reproductive and developmental (R/D) effects				
Long-term exposure	Limited evidence for reproductive effects.	---	---	---
Cancer				
Long-term exposure	Inadequate evidence, based on the lack of epidemiological studies.	---	---	---
Mortality				
Short-term	Inadequate, based on limited epidemiological studies.	Suggestive, but inconsistent evidence of a relationship for acute morbidity and mortality from respiratory and cardiovascular disease.	---	---
Long-term	Inadequate, based on the lack of epidemiological studies. There were no available studies examining long-term UFP exposure and total mortality.	---	---	---

--- Not evaluated, or there is no information available